Sirolimus- vs Paclitaxel-Eluting Stents in De Novo Coronary Artery Lesions

The REALITY Trial: A Randomized Controlled Trial

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Context Compared with bare metal stents, sirolimus-eluting and paclitaxel-eluting stents have been shown to markedly improve angiographic and clinical outcomes after percutaneous coronary revascularization, but their performance in the treatment of de novo coronary lesions has not been compared in a prospective multicenter study.

Objective To compare the safety and efficacy of sirolimus-eluting vs paclitaxel-eluting coronary stents.

Design Prospective, randomized comparative trial (the REALITY trial) conducted between August 2003 and February 2004, with angiographic follow-up at 8 months and clinical follow-up at 12 months.

Setting Ninety hospitals in Europe, Latin America, and Asia.

Patients A total of 1386 patients (mean age, 62.6 years; 73.1% men; 28.0% with diabetes) with angina pectoris and 1 or 2 de novo lesions (2.25-3.00 mm in diameter) in native coronary arteries.

Intervention Patients were randomly assigned in a 1:1 ratio to receive a sirolimus-eluting stent (n=701) or a paclitaxel-eluting stent (n=685).

Main Outcome Measures The primary end point was in-lesion binary restenosis (presence of a more than 50% luminal-diameter stenosis) at 8 months. Secondary end points included 1-year rates of target lesion and vessel revascularization and a composite end point of cardiac death, Q-wave or non–Q-wave myocardial infarction, coronary artery bypass graft surgery, or repeat target lesion revascularization.

Results In-lesion binary restenosis at 8 months occurred in 86 patients (9.6%) with a sirolimus-eluting stent vs 95 (11.1%) with a paclitaxel-eluting stent (relative risk [RR], 0.84; 95% confidence interval [CI], 0.61-1.17; $P=.31$). For sirolimus- vs paclitaxel-eluting stents, respectively, the mean (SD) in-stent late loss was 0.09 (0.43) mm vs 0.31 (0.44) mm (difference, –0.22 mm; 95% CI, –0.26 to –0.18 mm; $P<.001$), mean (SD) in-stent diameter stenosis was 23.1% (16.6%) vs 26.7% (15.8%) (difference, –3.60%; 95% CI, –5.12% to –2.08%; $P<.001$), and the number of major adverse cardiac events at 1 year was 73 (10.7%) vs 76 (11.4%) (RR, 0.94; 95% CI, 0.69-1.27; $P=.73$).

Conclusion In this trial comparing sirolimus- and paclitaxel-eluting coronary stents, there were no differences in the rates of binary restenosis or major adverse cardiac events.

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A REPORT IN JUNE 2002 OF A profoundly reduced 6-month restenosis rate among recipients of sirolimus-eluting stents for the treatment of de novo coronary lesions[1] was the first of a rapidly growing number of studies showing the safety and efficacy of this stent in the management of coronary artery disease.[2-5] Favorable clinical results were also reported with a paclitaxel-eluting stent, which uses a different drug, polymer, and drug-release kinetics.[6-9] The results of randomized trials comparing each of these drug-eluting stents with bare metal stents of identical or similar design indicate that the rate of late luminal loss is lower after implantation of sirolimus-eluting stent than paclitaxel-eluting stent.[10] However, differences in the populations studied, in implantation and angiographic techniques applied, and in methods of data analysis may not allow for legitimate comparisons of these different studies. Thus, a prospective, randomized

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comparison of sirolimus-eluting stent vs paclitaxel-eluting stent was warranted.

The objective of this study was to compare the safety and efficacy of the CYPHER sirolimus-eluting stent (Cordis Corp, Warren, NJ) and the TAXUS paclitaxel-eluting stent (Boston Scientific Corp, Natick, Mass) systems in a multicenter, randomized clinical trial in patients with de novo coronary artery lesions.

METHODS

Patient Enrollment

This prospective trial randomized 1386 patients between August 2003 and February 2004 at 90 centers in Europe, Latin America, and Asia. The protocol was reviewed and approved by the ethics committee of each participating medical institution. Prior to any test or procedure related to the trial, the benefits and risks of the study were explained and written informed consent was obtained from each participating patient. The patients enrolled in this trial were aged 18 years or older, presented with 1 or 2 de novo lesions 2.25 mm to 3.00 mm in diameter by visual estimate in 1 or 2 native coronary arteries, and stable or unstable angina pectoris, using the Canadian Cardiology Society (I-IV) and Braunwald (B and C, I-III) classifications,[11,12] or documented silent ischemia. One target lesion 15 mm or more and a second lesion 10 mm or more in length could be treated (without upper limit in lesion length), with visually estimated stenosis(es) between 51% and 99% and a Thrombolysis in Myocardial Infarction (TIMI) grade 1 or greater coronary flow designation for both lesions.

Patients were excluded from the trial if they (1) had a Q-wave or non–Q-wave myocardial infarction (MI) within 72 hours, with an initial creatine kinase level of more than twice the upper limit of normal and creatine kinase and creatine kinase–MB fraction persistently abnormal at the time of the procedure; (2) presented with Braunwald A I-II-III unstable angina; (3) had a more than 50% unprotected left main coronary stenosis or more than 50% stenoses of additional lesions proximal or distal to the target lesion; (4) had any target lesion containing a thrombus or calcifications that precluded successful predilatation or was totally occluded; (5) had a left ventricular ejection fraction of less than 25%; (6) had a serum creatinine level of more than 2.9 mg/dL (260 µmol/L) at the time of the procedure; or (7) had allergy to aspirin, clopidogrel, ticlopidine, heparin, stainless steel, contrast material, sirolimus, or paclitaxel. Contraindications to undergo coronary artery bypass graft surgery, pretreatment with methods other than balloon angioplasty, lesion tortuosity precluding proper stent delivery or deployment, prior stent implantation within 10 mm of the target lesion(s), previous brachytherapy, cardiac allograft, and life expectancy of less than 12 months were other possible reasons for exclusion from the trial.

Randomization Procedure

Following identification of a target lesion that met all eligibility criteria, patients received a unique study identification code and were randomly assigned on a 1:1 basis to receive 1 of the 2 study stents. Randomization was stratified according to participating site and number of lesions and concealed using a central telephone allocation service. All patients underwent protocol-mandated follow-up angiography at 8 months and were followed up clinically at 30 days and 8, 12, 18, and 24 months after the index procedure. This article reports the 8-month angiographic and 12-month clinical results (24-month follow-up is not yet available).

Procedural Techniques

Percutaneous vascular access was obtained according to each institution's standard procedures. After administration of nitrates, balloon predilatation of the target lesion was performed before delivery of 1 or more stents of sufficient length to completely cover the target lesions. The sirolimus-eluting stents were delivered on a Raptor Rapid Exchange (Cordis Corp) balloon catheter. The paclitaxel-eluting stents were delivered on a Maverick (Boston Scientific Corp) balloon catheter. The size of the sirolimus-eluting stent ranged between 8 mm and 33 mm in length and between 2.25 mm and 3.00 mm in diameter, while the size of the paclitaxel-eluting stent ranged between 8 mm and 32 mm in length and between 2.25 mm and 3.00 mm in diameter. Use of different drug-eluting stents in the same patient was not allowed.

Quantitative Coronary Angiography

An independent angiographic core laboratory (Cardialysis, Rotterdam, the Netherlands) analyzed all preprocedural, periprocedural, and postprocedural angiographic images using edge-detection techniques.[13] The core laboratory was blinded to the treatment assignment. (The 2 types of stent have a similar angiographic appearance.) Coronary luminal diameter and degree of stenosis (as a percentage of the diameter) were measured before dilatation, at the end of the procedure, and at the 8-month angiographic follow-up. Binary restenosis was defined as the presence of a more than 50% luminal-diameter stenosis. Late loss was calculated as the difference between minimum luminal diameter (MLD) immediately after the procedure and MLD measured at 8 months. The target lesion was defined as the stent segment and 5 mm proximal and distal to the edge of the stent.

Periprocedural and Long-term Antithrombotic Regimen

The following guidelines were specified by the protocol regarding the administration of antithrombotic medications:

Preprocedure. Treatment with aspirin began 12 hours or more before the procedure in a dose of at least 100 mg. Clopidogrel was administered before or immediately after the procedure in a loading dose of 300 mg followed by 75 mg once daily or in a maintenance dose of 75 mg for 3 or more days be-

fore the procedure. Alternatively, 2 doses of ticlopidine, 250 mg, were administered within 24 hours before the revascularization procedure.

Intraprocedure. Heparin was administered in boluses to reach and maintain an activated clotting time of more than 250 seconds. The use of glycoprotein IIb/IIIa inhibitors was left to investigators' discretion.

Postprocedure. Clopidogrel, 75 mg, was administered once daily, or ticlopidine, 250 mg, was administered twice daily.

Long-term. Aspirin, 100 mg/d, was administered indefinitely to all patients. Clopidogrel, 75 mg once daily, was administered for 6 months or more in the paclitaxel-eluting stent group and for 2 months or more in the sirolimus-eluting stent group. Alternatively, ticlopidine, 250 mg twice daily, was administered for 6 months or more in the paclitaxel-eluting stent group and for 2 months or more in the sirolimus-eluting stent group.

Patient Follow-up

All surviving patients were to have repeat angiography at 8 months ± 30 days of follow-up. Clinical follow-up visits were scheduled at 30 days, 8 months, and 12 months and included a physical examination at 8 months and, at all other time points, monitoring of cardioactive and antithrombotic drug use, interim hospitalizations, invasive or noninvasive diagnostic tests, and occurrence of major adverse cardiac events as well as stable or unstable angina according to the Canadian Cardiology Society and the Braunwald classifications.[11,12]

Prespecified Study End Points

The primary end point of the trial was the rate of binary in-lesion restenosis by quantitative coronary angiography (QCA) at 8 months after the index procedure.

The secondary end points of the trial included rates of target lesion revascularization (TLR); target vessel revascularization; target vessel failure, defined as cardiac death, MI, or target vessel revascularization; composite major adverse cardiac events, including cardiac death, Q-wave or non–Q-wave MI, emergent coronary artery bypass graft surgery, or repeat TLR; in-stent binary restenosis by QCA; and in-stent and in-lesion late loss by QCA, up to 8 months of follow-up. Additional secondary angiographic and procedural end points included in-stent and in-lesion MLD and percentage diameter stenosis by QCA immediately after the index procedure and at 8 months of follow-up; device success, defined as attainment of a final residual diameter stenosis of less than 30% by QCA, using the assigned device only; lesion success, defined as the attainment of less than 50% residual stenosis by QCA, using any percutaneous revascularization method; and procedure success, defined as attainment of less than 50% final diameter stenosis by QCA, using any percutaneous revascularization method, without death, MI, or repeat TLR during the index hospitalization. There were no prespecified subgroup analyses. Target lesion revascularization was considered clinically driven if prompted by symptoms consistent with myocardial ischemia, preceded by an abnormal stress test result consistent with myocardial ischemia, if there were other electrocardiographic changes consistent with myocardial ischemia, or if the lesion diameter stenosis was more than 70% at follow-up.

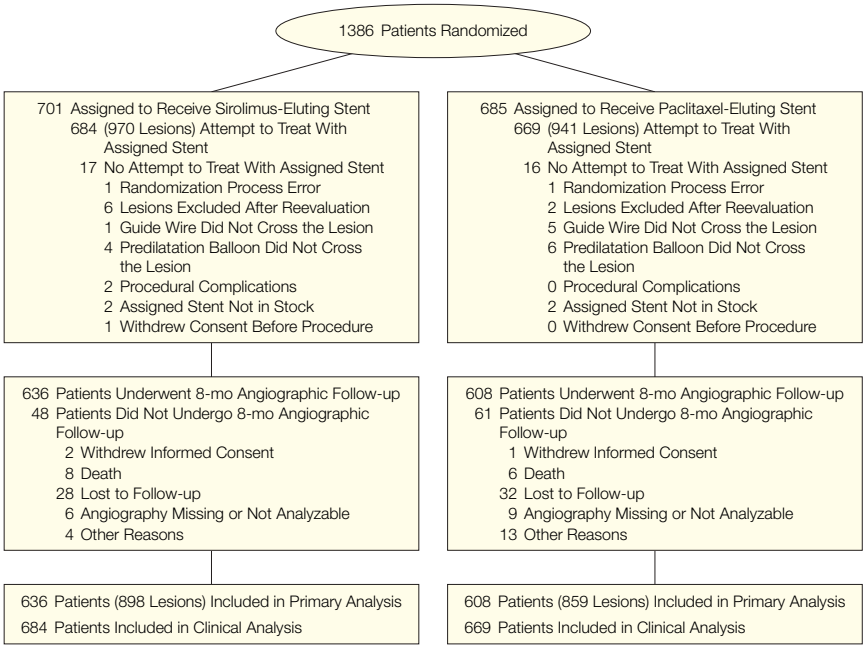
Definition of Stent Thrombosis

Stent thrombosis was defined as a composite, 30-day end point including death, Q-wave MI, or abrupt vessel closure requiring revascularization. Any death not attributed to a noncardiac cause in the first 30 days or any Q-wave MI in the territory of the stented vessel in the first 30 days was adjudicated as stent thrombosis. It was classified as acute if it occurred within the first 24 hours, subacute up to 30 days, and late after 30 days. Late thrombosis was defined as MI attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site more than 30 days after the index procedure in absence of an interim target vessel revascularization.

Trial Monitoring

A data and safety monitoring board was responsible for the review of data and

Figure 1. Flow of Patients Through the Trial



identification of potential safety issues. The members of this Board were not affiliated with the study sponsor and did not participate in the trial. Meetings of the board were planned regularly to allow the review of all reported major adverse cardiac events throughout the duration of the study. The data and safety monitoring board was unaware of the treatment assignment of individual patients.

A clinical events committee was composed of interventional and noninterventional cardiologists not associated with the sponsor. This committee developed specific criteria for the classification of major clinical events. The members of the committee were not provided with the treatment assignment of individual patients or the primary results of the trial. The committee met regularly to review and adjudicate all major clinical events, including stent thrombosis. All electrocardiograms related to clinical events and other pertinent data were adjudicated by the clinical events committee, who classified the MIs based on available data.

Statistical Analysis

The trial was designed with a 2-sided, $P<.05$ level of significance and 95% power to reject the null hypothesis of no difference between the 2 treatment groups. The assumptions used for the power calculations were a 14.0%, 8-month in-lesion restenosis rate with paclitaxel-eluting stent vs 8.0% with the sirolimus-eluting stent; ie, a 43% reduction in restenosis at 8 months with the sirolimus-eluting stent. The assumptions for the sirolimus-eluting stent were based on the results of the RAVEL,[1] SIRIUS,[2] and E-SIRIUS[3] studies, and for the paclitaxel-eluting stent on the results of the TAXUS-II trial[7] (the TAXUS-IV[8] results were not yet available at the time of our study design). Applying these assumptions, a sample size of 1476 lesions was estimated for the trial under the further assumption that complete 8-month follow-up information would be available for each patient in the study. The total sample size was increased to 2000 lesions (1334 patients), to account for 74% compliance with the 8-month angiographic follow-up, and an average of 1.5 lesions per patient. From the 1386 patients randomly assigned initially, 1353 (n=684 with a sirolimus-eluting stent and n=669 with a paclitaxel-eluting stent) were included in the analysis (FIGURE 1).

The protocol prespecified a modified intention-to-treat principle whereby only randomized patients who underwent an attempt to implant the assigned study stent were included in the analysis; this led to the exclusion of 17 patients allocated to sirolimus-eluting stent and 16 patients allocated to paclitaxel-eluting stent (Figure 1). In a sensitivity analysis of clinical outcomes specified post hoc, we included 684 patients allocated to sirolimus-eluting stent and 669 patients allocated to paclitaxel-eluting stent. Three patients had to be excluded from this post hoc analysis; 1 in each group had erroneously undergone randomization without giving written informed consent, and another patient allocated to sirolimus-eluting stent withdrew consent immediately after randomization. Ascertainment of angiographic outcomes was impossible in patients not attending follow-up angiography. This resulted in the additional exclusion of 48 patients allocated to sirolimus-eluting stent and 61 patients allocated

Table 1. Baseline Demographic and Clinical Characteristics*

Characteristics	Sirolimus-Eluting Stent (n = 684)	Paclitaxel-Eluting Stent (n = 669)	*P* Value
Age, mean (SD), y	62.6 (10.5)	62.6 (10.0)	.90
Men	507 (74.1)	482 (72.0)	.39
Medical history			
Diabetes mellitus	187 (27.3)	192 (28.7)	.59
Hypertension	448 (65.5)	452 (67.6)	.45
Hypercholesterolemia	497 (72.7)	468 (70.0)	.28
Stroke	29 (4.2)	30 (4.5)	.89
Congestive heart failure	25 (3.7)	18 (2.7)	.35
Family history of coronary artery disease	288 (4.2)	256 (38.4)	.17
Peripheral vascular disease	60 (88)	55 (8.2)	.77
Previous myocardial infarction	289 (42.3)	258 (38.6)	.18
Previous coronary artery bypass graft surgery	54 (7.9)	46 (6.9)	.53
Previous coronary angioplasty	159 (23.2)	136 (20.3)	.21
Smoking			
Previous	274 (40.2)	237 (35.4)	.07
Current	138 (20.2)	147 (22.0)	.46
Clinical presentation			
Unstable angina class†			
I	35 (5.1)	44 (6.6)	.30
II	108 (15.8)	109 (16.3)	.82
III	52 (7.6)	58 (8.7)	.49
Stable angina class†			
I	55 (8.0)	48 (7.2)	.61
II	241 (35.2)	218 (32.6)	.33
III	91 (13.3)	90 (13.5)	.94
IV	13 (1.9)	13 (1.9)	>.99
Silent ischemia	89 (13)	89 (13.3)	.94
No. of diseased coronary arteries			
1	331 (48.4)	322 (48.1)	.96
2	253 (37)	250 (37.4)	.91
3	96 (14.0)	94 (14.1)	>.99
4	4 (0.6)	3 (0.4)	>.99

*Data are reported as No. (%) of patients unless otherwise noted.
†According to the classifications of the Canadian Cardiology Society and Braunwald.[11,12]

to paclitaxel-eluting stent in the analysis of angiographic outcomes (Figure 1). (For the clinical analysis, patients followed up included those who did not undergo 8-month angiographic follow-up.)

The correlation of lesion characteristics within patients with multiple lesions had negligible effects on standard errors: the design factor for differences in in-lesion binary restenosis, defined as the robust standard error adjusted for the correlation of multiple lesions within a patient divided by the conventional standard error assuming no correlation, was 1.05.

Clinical events including death, MI, and revascularization are reported on a per-patient basis. For patients with multiple lesions, a failure of any lesion was counted toward the composite event rate. Differences between the treatment groups were examined by analysis of variance for continuous variables and by the Fisher exact test for categorical variables. The incidence of major adverse cardiac events during the follow-up period was analyzed using actuarial life-table methods. All statistical analyses were performed using SAS statistical software, version 8 (SAS Institute Inc, Cary, NC).

RESULTS

There were 684 patients with 970 lesions assigned to treatment with sirolimus-eluting stent and 669 patients with 941 lesions assigned to paclitaxel-eluting stent. Baseline characteristics are presented in TABLE 1. The mean age of the overall population was 62.6 years, 989 (73.1%) were men, and diabetes mellitus was present in 379 (28.0%). There were 769 patients (50%) who presented with stable angina, 406 (30%) had unstable angina, and the remainder had silent ischemia. There were no significant differences in these baseline characteristics between the 2 study groups.

Baseline Lesion Characteristics

TABLE 2 shows the lesion characteristics of the overall population and of each study group. There were no significant differences between the groups. Nearly 50% of the target lesions were located in the left anterior descending coronary artery, while nearly all other lesions were evenly distributed between the left circumflex and the right coronary arteries. The lesion length was more than 10 mm in three fourths and more than 20 mm in one fourth of lesions, and one third were moderately or heavily calcified.

Procedural Characteristics and Outcomes

A single stent was implanted in 546 patients (40%), 2 stents in 487 (36%), 3 stents in 206 (15%), and 4 or more stents in 111 (8%) in both study groups (mean, 1.9 stents per patient and 1.4 stents per lesion). The mean stent diameter was 2.8 mm in both groups, and the mean length was 22.8 mm in the sirolimus-eluting stent group and 23.5 mm in the paclitaxel-eluting stent group. The maximum dilatation pressure during stent implantation was significantly lower in the paclitaxel-eluting stent group than the sirolimus-eluting stent group. Other procedural characteristics, including prestent angioplasty, total stent length, postprocedure TIMI grade, rates and types of postprocedure intimal dissection, and use of glycoprotein IIb/IIIa inhibitors during the procedure, were similar in both study groups (TABLE 3).

Table 2. Baseline Lesion Characteristics

Characteristics	No./Total (%) of Lesions: Sirolimus-Eluting Stent (n = 970 Lesions)	No./Total (%) of Lesions: Paclitaxel-Eluting Stent (n = 941 Lesions)	Difference, % (95% Confidence Interval)	*P* Value
No./total (%) of patients with >1 lesion	270/684 (39.5)	254/669 (38.0)	1.5 (–3.7 to 6.7)	.58
Lesion location				
Left anterior descending artery	484 (49.9)	453 (48.1)	1.8 (–2.7 to 6.2)	.46
Left circumflex artery	242 (24.9)	278 (29.5)	–4.6 (–8.6 to 0.6)	.03
Right coronary artery	240 (24.7)	207 (22.0)	2.7 (–1.0 to 6.5)	.16
Left main coronary artery	4 (0.4)	2 (0.2)	0.2 (–0.3 to 0.7)	.69
Coronary graft*	0	1 (0.1)	–0.1 (–0.3 to 0.1)	.49
Preprocedural TIMI grade				
0	6 (0.6)	7 (0.8)	–0.1 (–0.9 to 0.6)	.79
1	33 (3.4)	30 (3.2)	0.2 (–1.4 to 1.8)	.90
2	96 (10.0)	111 (11.9)	–2.0 (–4.8 to 0.9)	.19
3	829 (86.0)	784 (84.1)	1.9 (–1.3 to 5.1)	.27
Lesion length, mm				
<10	235 (25.4)	208 (23.2)	2.1 (–1.8 to 6.1)	.30
10-20	439 (47.4)	443 (49.4)	–2.1 (–6.7 to 2.5)	.40
>20	253 (27.3)	245 (27.3)	–0.1 (–4.1 to 4.0)	>.99
Lesion angulation				
None	777 (83.8)	734 (82.0)	1.8 (–1.6 to 5.3)	.32
Moderate	150 (16.2)	161 (18.0)	–1.8 (–5.3 to 1.6)	.32
Ostial lesion	33/927 (3.6)	29/895 (3.2)	0.3 (–1.3 to 2.0)	.80
Moderate to heavy calcification	340/928 (36.6)	295/899 (32.8)	3.8 (–0.5 to 8.2)	.09
Bifurcation or side branch lesion				
No major branch involvement	562 (60.6)	546 (60.9)	–0.3 (–4.8 to 4.2)	.92
Bifurcation requiring double guide wire	365 (39.4)	350 (39.1)	0.3 (–4.2 to 4.8)	.92
Lesion type*				
A	39 (4.0)	38 (4.1)	0.0 (–1.8 to 1.7)	>.99
B1	89 (9.2)	89 (9.5)	–0.3 (–2.9 to 2.3)	.81
B2	583 (60.5)	559 (60.0)	0.5 (–3.9 to 4.9)	.85
C	253 (26.2)	246 (26.4)	–0.2 (–4.1 to 3.8)	.96

*American College of Cardiology/American Heart Association classification.

Table 3. Procedural Characteristics

Characteristics	Sirolimus-Eluting Stent (n = 970 Lesions)	Paclitaxel-Eluting Stent (n = 941 Lesions)	Difference (95% Confidence Interval)	*P* Value
Direct stenting, No./total (%) of lesions	242/967 (25.0)	220/939 (23.4)	1.6 (–2.2 to 5.4)	.42
Maximum pressure during stent placement, mean (SD), bars	14.6 (3.0)	14.2 (3.2)	0.5 (0.2 to 0.8)	<.001
Total stent length, mean (SD), mm	22.8 (11.8)	23.5 (11.4)	–0.8 (–1.8 to 0.3)	.15
Poststent balloon dilatation, No. (%) of lesions	345 (35.6)	325 (34.5)	1.0 (–3.3 to 5.3)	.67
Nominal diameter, mean (SD), mm	2.96 (0.42)	2.92 (0.44)	0.04 (–0.03 to 0.10)	.24
Maximum pressure, mean (SD), bars	15.4 (4.0)	14.7 (4.2)	0.7 (0.1 to 1.4)	.02
Postprocedure dissection type, No. (%) of lesions*				
No dissection	936 (97.0)	911 (97.2)	–0.2 (–1.7 to 1.3)	.79
A	8 (0.8)	12 (1.3)	–0.5 (–1.4 to 0.5)	.37
B	13 (1.3)	9 (1.0)	0.4 (–0.6 to 1.3)	.52
C	8 (0.8)	3 (0.3)	0.5 (–0.2 to 1.2)	.23
Other type	0	2 (0.2)	–0.2 (–0.5 to 0.1)	.24
Glycoprotein IIb/IIIa inhibitors during procedure, No./ total (%) of patients	106/684 (15.5)	103/668 (15.4)	0.1 (–3.8 to 3.9)	>.99
Hospital stay, mean (SD), d	2.8 (1.7)	2.9 (2.2)	–0.2 (–0.4 to 0.1)	.14

*National Heart, Lung, and Blood Institute classification.

Procedural Success and Quantitative Coronary Angiography

There were no differences between the 2 study groups in mean lesion length, preprocedure reference vessel diameter, percentage diameter stenosis, or minimum luminal diameter. There was no significant difference in the delivery success of the 2 devices. More than 94% of lesions were successfully treated with the assigned stent in both study groups, and ultimately, less than 50% residual stenosis using any percutaneous revascularization method was achieved in nearly 100% of the stented lesions (TABLE 4).

The mean in-lesion binary restenosis rate, the primary study end point, was 9.6% (n = 86)in the sirolimus-eluting stent group vs 11.1% (n = 95) in the paclitaxel-eluting stent group, a difference that did not reach statistical significance (relative risk, 0.84; 95% confidence interval, 0.61-1.17; *P* = .31). However, significant differences were observed between the 2 groups in some immediate outcomes ascertained by QCA. In particular, the postprocedure mean in-stent minimum luminal diameter was significantly smaller, and in-stent percentage diameter stenosis was significantly greater in the sirolimus-eluting stent group than in the paclitaxel-eluting stent group. Despite this, at 8 months, QCA measurements, available for 1244 (91.9%) of 1353 patients and for 1754 (91.7%) of 1911 lesions, showed significant differences in MLD, absolute gain, late loss, and late loss index, all favoring the sirolimus-eluting stent (Table 4).

A sensitivity analysis of clinical outcomes based on 699 patients allocated to sirolimus-eluting stent and 684 patients allocated to paclitaxel-eluting stent yielded nearly identical results.

Short- and Long-term Adverse Clinical Events

Death, Q-wave or non–Q-wave MI, and surgical or percutaneous TLR occurred during hospitalization in 4 (0.6%), 29 (4.2%), and 3 (0.4%) patients, respectively, in the group assigned to sirolimus-eluting stent vs 2 (0.3%), 31 (4.6%), and 1 (0.1%) patients, respectively, in the group assigned to paclitaxel-eluting stent. The overall rate of in-hospital major adverse cardiac events was 4.5% in the sirolimus-eluting stent group vs 4.9% in the paclitaxel-eluting stent group. These differences were not statistically significant. Likewise, there were no significant differences between the 2 study groups in rates of other in-hospital adverse clinical events, including target vessel revascularization, stent thrombosis, cerebrovascular events, and hemorrhagic complications.

The overall, 12-month cumulative rate of major adverse cardiac events was 10.7% (n = 73) in the sirolimus-eluting stent group vs 11.4% (n = 76) in the paclitaxel-eluting stent group (TABLE 5 and FIGURE 2). The overall incidence of TLR was 6.0% (n = 41) in the sirolimus-eluting stent group vs 6.1% (n = 41) in the paclitaxel-eluting stent group. In the sirolimus-eluting stent group, 50.0% of all TLRs were clinically driven vs 54.3% of TLRs in the paclitaxel-eluting stent group. These differences were not statistically significant. Among other adverse clinical events, there were no differences between the 2 groups in rates of target vessel revascularization, target vessel failure, subacute occlusion, cerebral vascular accidents, or hemorrhagic complications. There were 5 stent thromboses (0.7%) in the sirolimus-eluting stent group vs 13 stent thromboses (1.9%) in the paclitaxel-eluting stent group, a difference that nearly reached statistical significance (*P* = .06 by Fisher exact test).

Compliance With Antiplatelet Drug Regimen

The overall mean (SD) duration of antiplatelet therapy was 175 (74) days in the sirolimus-eluting stent group vs 204 (47) days in the paclitaxel-eluting stent group (*P* < .001). At the time of discharge from the hospital, 96.8% and 97.0% of patients in the sirolimus-eluting stent and paclitaxel-eluting stent groups, respectively, were treated with doses of clopidogrel or ticlopidine according to the protocol-mandated guidelines. Corresponding values were 95.9% and 97.6% of patients at 1 month and 48.8% and 52.5% of patients at 8 months of follow-up. These differences in treatment adherence rates

between the 2 groups were not statistically significant.

COMMENT

The REALITY trial is the first large, randomized, multicenter trial to directly compare the clinical and angiographic results after percutaneous myocardial revascularization with a sirolimus-eluting stent vs a paclitaxel-eluting stent in a population of patients with de novo coronary artery stenoses. The baseline clinical and angiographic characteristics of the study population were consistent with those found in other interventional studies of angioplasty with or without stent implantation for single- or multivessel coronary artery disease outside of the acute phase of MI, including nearly 30% with diabetes. In addition, the mean reference vessel diameter in this study (2.40 mm) was smaller than in the SIRIUS[2] (2.80 mm) or the TAXUS-IV[8] (2.75 mm) trials.

Early Results

From a procedural standpoint, this study demonstrated a similarly high deliverability of both stents and similar immediate procedural outcomes in both study groups. However, the angiographic measurements made immediately after stent implantation suggested a slightly larger lumen of the paclitaxel-eluting stent than that of the sirolimus-eluting stent, despite the use of a higher maximum dilatation pressure with the latter, perhaps because of a greater compliance of the balloon used to deploy the TAXUS stent. As observed in earlier trials comparing each stent type with their bare metal counterparts, the rates of procedural and in-hospital complications were low and similar in both study groups.

Long-term Angiographic Results

At the 8-month angiographic follow-up, significant differences were found in in-stent MLD, percentage diameter stenosis, in-stent late loss, and in-stent late loss index, all favoring the sirolimus-eluting stent. These observations indicate a significantly greater

Table 4. Results of Quantitative Coronary Analysis at Baseline and at 8-Month Follow-up*

	Sirolimus-Eluting Stent (n = 970 Lesions)	Paclitaxel-Eluting Stent (n = 941 Lesions)	Difference (95% Confidence Interval)	*P* Value
Preprocedure, mean (SD)				
Lesion length, mm	16.96 (10.04)	17.31 (10.09)	–0.35 (–1.28 to 0.58)	.47
Reference vessel diameter, mm	2.40 (0.48)	2.40 (0.48)	0.00 (–0.05 to 0.04)	.97
Diameter stenosis, %	61.21 (12.26)	61.43 (11.75)	–0.22 (–1.30 to 0.87)	.70
Minimum luminal diameter, mm	0.92 (0.31)	0.91 (0.32)	0.00 (–0.03 to 0.03)	.98
Postprocedure				
Success				
Device, No. (%) of lesions	914 (94.3)	903 (96.3)	–1.9 (–3.8 to –0.0)	.05
Lesion, No. (%) of lesions	964 (99.4)	933 (99.4)	0.00 (–0.7 to 0.7)	>.99
Procedure, No. (%) of patients	649 (94.9)	631 (94.5)	0.4 (–2.0 to 2.8)	.81
Angiographic measurements, mean (SD)				
In-stent minimum luminal diameter, mm	2.08 (0.35)	2.16 (0.37)	–0.08 (–0.11 to 0.05)	<.001
In-lesion minimum luminal diameter, mm	1.83 (0.39)	1.86 (0.41)	–0.03 (–0.06 to 0.01)	.12
Diameter stenosis, %				
In-stent	15.96 (6.91)	15.00 (7.49)	0.95 (0.31 to 1.60)	.004
In-lesion	23.58 (8.78)	23.85 (9.52)	–0.27 (–1.10 to 0.55)	.52
8-mo angiographic follow-up				
Binary restenosis, No. (%) of lesions				
In-stent	63 (7.0)	71 (8.3)	0.86 (0.65 to 1.14)†	.32
In-lesion	86 (9.6)	95 (11.1)	0.84 (0.61 to 1.17)†	.31
Other angiographic measurements, mean (SD)				
Minimum luminal diameter, mm				
In-stent	2.00 (0.54)	1.85 (0.52)	0.14 (0.09 to 0.19)	<.001
In-lesion	1.79 (0.51)	1.71 (0.49)	0.09 (0.04 to 0.13)	<.001
Diameter stenosis, %				
In-stent	23.11 (16.59)	26.71 (15.83)	–3.60 (–5.12 to –2.08)	<.001
In-lesion	29.11 (15.81)	31.06 (15.36)	–1.95 (–3.41 to –0.49)	.009
Late loss, mm				
In-stent	0.09 (0.43)	0.31 (0.44)	–0.22 (–0.26 to –0.18)	<.001
In-lesion	0.04 (0.38)	0.16 (0.40)	–0.11 (–0.15 to –0.08)	<.001
In-stent late loss index, %	0.08 (0.44)	0.26 (0.42)	–0.18 (–0.22 to –0.1.9)	<.001

*Device success was defined as attainment of a final residual diameter stenosis less than 30% using the assigned device only. Lesion success was defined as attainment of less than 50% residual stenosis using any percutaneous revascularization method. Procedure success was defined as attainment of less than 50% final diameter stenosis using any percutaneous revascularization method, without death, myocardial infarction, or repeat target lesion revascularization during the index hospitalization. In-stent measurements were made within the struts of the stent. Late loss is the difference between postprocedure and follow-up minimum luminal diameter. The late loss index is the quotient of late loss and absolute gain.

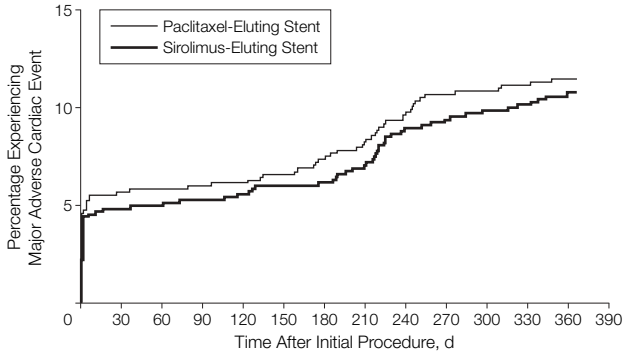
†Data are relative risk (95% confidence interval).

Table 5. Major Adverse Clinical Events During 12 Months of Follow-up*

	No. (%) of Patients			
	Sirolimus-Eluting Stent (n = 684)	Paclitaxel-Eluting Stent (n = 669)	Relative Risk (95% Confidence Interval)	*P* Value
Major adverse cardiac events†				
Death	16 (2.3)	9 (1.3)	1.74 (0.77-3.91)	.23
Cardiac	10 (1.5)	7 (1.0)	1.40 (0.54-3.65)	.63
Noncardiac	6 (0.9)	2 (0.3)	2.93 (0.59-14.49)	.29
Myocardial infarction	35 (5.1)	40 (6.0)	0.86 (0.55-1.33)	.55
Q-wave	1 (0.1)	8 (1.2)	0.12 (0.02-0.97)	.02
Non–Q-wave	34 (5.0)	32 (4.8)	1.04 (0.65-1.66)	.90
Target lesion revascularization	41 (6.0)	41 (6.1)	0.98 (0.64-1.49)	>.99
Surgical	4 (0.6)	6 (0.9)	0.65 (0.18-2.30)	.54
Percutaneous	37 (5.4)	38 (5.7)	0.95 (0.61-1.48)	.91
Overall	73 (10.7)	76 (11.4)	0.94 (0.69-1.27)	.73
Other adverse clinical events				
Target vessel revascularization‡	14 (2.0)	12 (1.8)	1.14 (0.53-2.45)	.84
Surgical	4 (0.6)	2 (0.3)	1.96 (0.36-10.64)	.69
Percutaneous	10 (1.5)	10 (1.5)	0.98 (0.41-2.33)	>.99
Target vessel failure	82 (12.0)	86 (12.9)	0.93 (0.70-1.24)	.68
Stent thrombosis	5 (0.7)	13 (1.9)	0.37 (0.13-0.49)	.06
Acute	2 (0.3)	4 (0.6)	0.49 (0.09-2.66)	.45
Subacute	3 (0.4)	7 (1.0)	0.42 (0.11-1.61)	.22
Late	0	2 (0.3)	. . .‖	.15
Cerebrovascular accident	4 (0.6)	6 (0.9)	0.65 (0.18-2.30)	.54
Hemorrhage	35 (5.1)	39 (5.8)	0.88 (0.56-1.37)	.63
Major	9 (1.3)	14 (2.1)	0.63 (0.27-1.44)	.30
Minor	27 (3.9)	26 (3.9)	1.02 (0.60-1.72)	>.99
Major vascular complications	15 (2.2)	20 (3.0)	0.73 (0.38-1.42)	.39

*Target vessel failure was defined as cardiac death, myocardial infarction, or target vessel revascularization. Stent thrombosis was defined as a composite 30-day end point attributable to cardiac ischemic events, including cardiac death, Q-wave myocardial infarction, or vessel closure requiring revascularization. Acute thrombosis was defined as thrombosis occurring on the day of or the day after the index procedure. Subacute thrombosis was defined as thrombosis occurring between 2 and 30 days after the index procedure. Late thrombosis was defined as myocardial infarction in the territory of the target vessel, with angiographic documentation of thrombus or total occlusion at the target site more than 30 days after the index procedure, in absence of an interim target vessel revascularization.
†Clinically driven.
‡Not involving target lesion.
‖Ellipses indicate too few data to calculate relative risk.

Figure 2. Kaplan-Meier 12-Month Actuarial Incidence of Major Adverse Cardiac Events



No. at Risk					
Paclitaxel-Eluting Stent	669	625	619	594	493
Sirolimus-Eluting Stent	684	648	640	617	505

degree of suppression of neointimal hyperplasia achieved by the sirolimus-eluting stent, particularly considering the smaller mean vessel diameter measured immediately after the implantation of sirolimus-eluting stent. However, the significant differences in several continuous angiographic variables, most importantly in-stent late loss, did not translate into significant differences in in-lesion binary restenosis or in TLR.

The discordance between late loss and binary restenosis at 8 months is probably multifactorial. First, immediately after stent deployment, a smaller MLD was achieved with the sirolimus-eluting stent than with the paclitaxel-eluting stent. Although the mean difference of 0.08 mm might seem trivial, it is of the same magnitude as the mean 0.09-mm total in-stent late loss observed with the sirolimus-eluting stent and might therefore have represented a notable handicap for this stent. Second, the relationship between late loss and binary restenosis is nonlinear and has been characterized by a curvilinear function.[14] The observed late loss values for both sirolimus-eluting stent and paclitaxel-eluting stent are located on the left of the curve, near an x-axis value of 0, where its slope is shallow. Furthermore, binary restenosis is by definition a dichotomous variable, which is only declared when a threshold of 50% diameter stenosis is reached, below which there is no further discrimination. Third, the large experience gained with bare metal stenting has confirmed that differences in stent performance are more pronounced when the lesions are more complex and when the patients are at higher baseline risk of developing restenosis.[15,16] Since patients with complex lesions and at higher periprocedural risk are generally less likely to be enrolled into randomized trials, those enrolled in the REALITY trial had only moderately complex lesions. Nearly 50% of the patients had single-vessel disease, the majority of lesions ranged between 10 mm and 20 mm in length, and the predominant lesion type was B2. These charac-

teristics probably reduced the likelihood of identifying a difference in performance between the 2 stents.

Long-term Clinical Results

The 12-month rates of major adverse cardiac events were similarly low in both study groups, confirming the excellent performance of both stents. In particular, there was no statistically significant difference in any of the major clinical events, including death, MI, and TLR. A longer follow-up may be required for the difference in late loss to translate into a significant difference in event rates. It is conceivable that a 12-month follow-up was not sufficient to unmask the importance of suppression or delay of neointimal hyperplasia.

In contrast with the results of other studies,[17,18] the rates of stent thrombosis in this study were similar in both groups. Since late stent thrombosis is a rare event, larger trials or meta-analyses will be needed to determine whether the trends observed in single studies or registries are the expression of a worrisome adverse clinical event.

Comparison With Similar Studies

The TAXi study randomly assigned 202 consecutive patients to the implantation of sirolimus-eluting stent vs paclitaxel-eluting stent.[19] At 6 months, there was no difference in major adverse cardiac events, defined as death, MI, and TLR, though the study was prematurely terminated and limited by a small patient population. More recently, the results of ISAR-DESIRE,[20] ISAR-DIABETES,[21] and SIRTAX,[22] which directly compared sirolimus-eluting stent with paclitaxel-eluting stent, were presented. Unlike the REALITY trial, these studies showed a clear and statistically significant superiority of sirolimus-eluting stent in the primary end points; namely, in-segment restenosis, in-segment late loss, and the composite of death, MI, and TLR, respectively. Importantly, these trials differ from REALITY by having enrolled patients with higher lesion complexity (exclusively in-stent restenosis in ISAR-DESIRE) or patients with specific and prorestenotic comorbidity (exclusively patients with diabetes in ISAR-DIABETES) or by an enrollment unlimited by exclusion criteria (SIRTAX). Each study was conducted in no more than 5 medical centers, in contrast with the 90 worldwide centers that participated in REALITY. The lower risk profile and lower risk of restenosis among the patients enrolled in the REALITY trial, together with an inevitable variability in interventional techniques, may have contributed to the smaller-than-expected difference in the primary end point.

A recently published meta-analysis of the results of 6 completed clinical trials, in which a total of 3669 patients were randomly assigned to sirolimus-eluting stent vs paclitaxel-eluting stent, found significant differences in rates of restenosis (9.3% vs 13.1%; $P<.001$) and TLR (5.1% vs 7.8%; $P<.001$) favoring the sirolimus-eluting stent.[23] No significant differences were found in mortality, MI, or stent thrombosis between the study groups.

Limitations

As is the case with nearly all randomized trials, several enrollment exclusion criteria created a selected patient population. Consequently, the observations made in the REALITY trial apply mostly to patients treated for 1 or 2 de novo lesions in small to moderately sized coronary arteries. Other ongoing trials that enroll mostly patients with diabetes, patients with in-stent restenosis or bifurcated or very long lesions, or patients with acute MI will help define the role of sirolimus-eluting stent vs paclitaxel-eluting stent in the overall percutaneous management of coronary artery disease. The respective contributions of these studies and of the REALITY trial should be viewed as complementary and not as competitive or necessarily discordant.

CONCLUSION

In this multicenter randomized comparison of sirolimus-eluting stent vs paclitaxel-eluting stent in patients with 1 or 2 de novo lesions in relatively small coronary arteries, no statistically significant difference was observed in the rate of binary in-lesion restenosis at 8 months, although QCA measurements indicated a more profound inhibition of neointimal hyperplasia by sirolimus-eluting stent. A longer follow-up may be required for the different degrees of neointimal proliferation suppression to translate into significantly different rates of binary restenosis or adverse clinical events.

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Gerrit-Anne Van Es, PhD, director of Research and Development for Cardialysis, Rotterdam, the Netherlands, an independent clinical research and data management organization, and Eric van Remortel, an employee of Cardialysis, maintained the entire trial database, completed an independent statistical review of every data point, and provided reports to the sponsor. Cardialysis received compensation for data management and statistical analysis, but Dr Van Es did not receive personal compensation for his role in this trial.
Independent Statistical Review: Christophe E. Minder, PhD, professor of Medical Statistics at the University of Bern, Switzerland, and Peter Jüni, MD, senior lecturer in Clinical Epidemiology at the University of Bern, received a complete copy of the raw data from Cordis Corporation and performed an independent statistical analysis. They received no compensation for this work and had no conflicts of interest, not receiving any type of payment, equity, or reimbursement from either of the companies manufacturing the stents compared in the trial. They confirmed that they were able to replicate the analyses of the primary angiographic and secondary clinical outcomes reported in the manuscript and that they consider the analyses to be appropriate.
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